Xofluza (Baloxavir Marboxil) for the Treatment Of Acute Uncomplicated Influenza

Kimberly E. Ng, PharmD, BCPS

INTRODUCTION

Influenza is caused by two main types of virus, type A and type B. Each year, it is easily spread via droplets or contact with the flu virus on surfaces, then transferred to the mouth, nose, or eyes. Those people who are infected are most contagious in the first three to four days when the illness begins but they can infect others one day before the onset of symptoms and up to seven days after becoming infected.[1] Symptoms of the flu, which include fever, body aches, chills, fatigue, and headache, can begin anywhere from 1 to 4 days after being infected.[2,3]

Influenza activity during the 2017–2018 season was high, with an estimated 48.8 million people becoming ill, including 959,000 hospitalizations and 79,400 deaths. Influenza A (H3N2) viruses were predominant for the entire season, whereas influenza B viruses were more commonly reported in March of 2018.[4] Influenza virus has the ability to change in two different ways, via either antigenic drift or antigenic shift. This allows the virus to cause illness in a person who may have already been infected and have developed antibodies against the virus. Influenza A viruses can undergo both antigenic drift and antigenic shift, whereas influenza B virus typically undergoes antigenic drift. Antigenic drifts are small changes in influenza genes that occur as the virus replicates. These viruses share antigenic properties so that an immune system is able to recognize and respond to them. Antigenic shift is a major change in the influenza A virus, resulting in new hemagglutinin and/or new hemagglutinin and neuraminidase proteins. The resulting new subtype is so different that most people do not have immunity so the virus could therefore quickly cause a pandemic. Because of the evolving nature of the influenza virus, flu vaccine composition is reviewed on a yearly basis and is modified to protect against the most common strains of the virus.[5]

The most effective way to prevent seasonal flu is to get vaccinated each year. The Centers for Disease Control and Prevention (CDC) recommends that unless contraindicated, everyone aged 6 months and older should receive an annual influenza vaccination. The 2018–2019 trivalent vaccine is composed of A/Michigan/45/2015 (H1N1) pdm09–like virus, A/Singapore/INFIMH-16-0019/2016 (H3N2)–like virus, and B/Colorado/06/2017–like virus (Victoria lineage). The quadrivalent vaccines also have the B/Phuket/3073/2013–like virus (Yamagata lineage).[6,7]

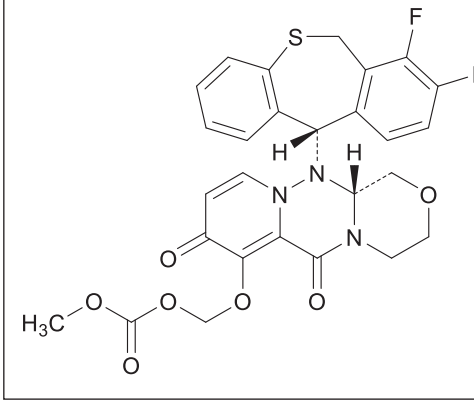
For those infected with influenza despite receiving the vaccination, antiviral neuraminidase inhibitors including oseltamivir, zanamivir, and peramivir can be used for treatment. Because of resistance to the adamantine class of antiviral drugs (amantadine and rimantadine), their use is not recommended in the United States.[8] Of the three neuraminidase inhibitors, oseltamivir, approved in 1999, is commonly prescribed. It is indicated for the treatment of acute, uncomplicated influenza A and B in patients 2 weeks of age and older who have been symptomatic for no more than 48 hours. It is also indicated as prophylaxis for influenza A and B in patients aged 1 year and older.[9] Unfortunately, oseltamivir resistance is possible. The H275Y mutation confers oseltamivir resistance in 2009 H1N1 flu viruses, thereby preventing oseltamivir from inhibiting neuraminidase activity and ultimately resulting in treatment failure. Because of the potential for drug resistance and treatment failure, a novel antiviral treatment has been developed and approved by the FDA.

Xofluza (baloxavir marboxil) is a new antiviral agent for influenza treatment approved by the FDA on October 24, 2018.[10] It is indicated for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours. Influenza virus has the ability to change over time as a result of mutation, virus type or subtype, resistance, or changes in virulence, and can therefore diminish the benefits of antivirals. Practitioners should treat patients based on drug susceptibility patterns for current strains of influenza. This article reviews the pharmacology, pharmacokinetics, clinical efficacy, dosage and administration, safety profile, and place in therapy of baloxavir.[11]

PHARMACOLOGY

Baloxavir marboxil is a prodrug that is converted by hydrolysis to baloxavir, the active form. Baloxavir inhibits the endonuclease activity of the polymerase acidic (PA) protein found in influenza virus to ultimately inhibit virus replication.[11]

Figure 1 Chemical Structure of Baloxavir



Dr. Ng is an Assistant Professor at St. John's University College of Pharmacy and Health Sciences in Queens, New York. Drug Forecast *is a regular column coordinated by Alan Caspi, PhD, PharmD, MBA, President of Caspi and Associates in New York, New York.*

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PHARMACOKINETICS

The pharmacokinetic parameters of baloxavir were evaluated in healthy subjects. Baloxavir marboxil is completely converted to its active metabolite, baloxavir.[11]

Absorption and Distribution

Baloxavir has a volume of distribution (Vd) of 1,180 liters (L). The time to maximum concentration is four hours. The drug can be taken with or without food, but food decreases the maximum plasma concentration (C_{max}) by 48% and area under the plasma drug concentration-time curve (AUC) by 36%. Baloxavir exhibits protein binding of approximately 93%.[11]

Metabolism and Elimination

Baloxavir is metabolized via UGT1A3 with a minor contribution from CYP3A4. Its half-life is 79.1 hours and clearance is 10.3 L/hr. After administering radiolabeled baloxavir marboxil, it was primarily excreted through feces (80.1%) with the remainder excreted through urine (14.7%), 3.3% as baloxavir.

Analyses did not identify an effect of renal function on pharmacokinetics in patients with a creatinine clearance (CrCl) of 50 mL/min and above. Severe renal impairment was not evaluated on baloxavir marboxil or the active metabolite. Patients with severe hepatic impairment were not evaluated. There were no differences in pharmacokinetics for those patients with moderate hepatic impairment (Child-Pugh class B).[11]

DOSAGE

Treatment should be initiated within 48 hours of symptom onset. It is taken orally as a single dose with or without food but should not be taken with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids, or oral supplements. Baloxavir is dosed based upon weight, as seen in Table 1.[11]

CLINICAL TRIALS

Baloxavir's clinical efficacy and safety in treating acute uncomplicated influenza was studied in one phase 2 trial and two phase 3 trials.

Phase 2 Trial

The phase 2 trial was a double-blind, placebo-controlled, dose-ranging, randomized trial in which 10, 20, or 40 mg of baloxavir or placebo were administered to Japanese adults aged 20 to 64 years old. Patients enrolled had fever, at least one respiratory symptom of moderate severity, and a symptom duration of no more than 48 hours. An entry criterion for the trial was a positive rapid antigen test. Of the 400 patients who underwent randomization, 389 completed the trial. A majority of patients were infected with influenza A (H1N1) pdm09 virus. The median time to alleviation of symptoms for each baloxavir-dose group was 54.2 hours in the 10-mg group, 51.0 hours in the 20-mg group, and 49.5 hours in the 40-mg group. This was significantly shorter than the placebo group (77.7 hours). All three baloxavir groups also had significantly greater reductions in influenza virus titers on days 2 and 3 compared to the placebo group. Adverse events were reported in 23%–27% of patients in the baloxavir groups and in 29% of patients in the placebo group. Four of 182 baloxavir recipients were found to have post-treatment viruses with PA amino acid substitutions.[12]

Table 1 Baloxavir Dosing in Adults and Adolescents Aged 12 Years and Older

Patient Body Weight (Kg)	Recommended Oral Dose
40 kg to less than 80 kg	Single dose of 40 mg
At least 80 kg	Single dose of 80 mg

CAPSTONE 1

The phase 3 trial was a double-blind, placebo- and oseltamivir-controlled, randomized trial that enrolled patients aged 12 to 64 years old with influenza-like illness, from the United States and Japan. Patients aged 20 to 64 years old received a single oral dose of baloxavir (40 mg for patients weighing < 80 kg or 80 mg for those weighing > 80 kg), or oseltamivir 75 mg twice daily for five days, or match placebos. Patients aged 12 to 19 years old randomly received either baloxavir or placebo on day one. The median time to alleviation of symptoms was shorter in the baloxavir group than in the placebo group in both adolescents (38.6 hours; $P = 0.006$) and adults (25.6 hours, $P < 0.001$). The difference in the time to alleviation of symptoms between the baloxavir group and the placebo group was greater in patients who initiated treatment within 24 hours after symptom onset (32.8 hours, $P < 0.001$) than in those who initiated treatment after 24 hours (13.3 hours, $P = 0.008$). The median time to alleviation of symptoms was similar in the baloxavir (53.5 hours) and oseltamivir (53.8 hours) groups. The median time to the resolution of fever and return to usual health was shorter with baloxavir than with placebo. Baloxavir was associated with rapid declines in infectious viral load compared to placebo and oseltamivir. After day 1, the median reductions from baseline were 4.8, 2.8, and 1.3 $\log_{10}TC1D_{50}$ per milliliter in the baloxavir, oseltamivir, and placebo groups. It was also found that PA138T/M amino acid substitutions were detected in 9.7% of 370 baloxavir recipients typically at day 5 or later, but they were not detected in the 95 randomly selected placebo recipients. Infectious virus was detected on day 5 in 7% of baloxavir recipients. The median time to the alleviation of symptoms was longer in baloxavir recipients with PA I38T/M substitutions than in those without variants.[12]

CAPSTONE 2

This phase 3, randomized, double-blind trial looked at baloxavir compared with placebo or oseltamivir in patients with influenza who were at high risk for influenza complications. Inclusion criteria were age ≥ 12 years, fever with influenza symptoms of ≤ 48 hours' duration, and the presence of at least one high-risk factor adapted from CDC criteria. The primary outcome was time to improvement of influenza symptoms. Secondary outcomes included infectious virus detection in serial nasopharyngeal swabs, prescription of antibiotics, and influenza-related complications. Results of this trial have not yet been published but they were presented as an oral abstract session at IDWeek 2018. The most common risk factors of the 2,184 randomized patients were asthma or chronic lung disease. The time to improvement of symptoms was shorter in the baloxavir group than in the placebo group (median, 73.2 hours vs. 102.3 hours, $P < 0.0001$) and shorter than in the oseltamivir group (81.0 hours, $P = 0.8347$). Patients with influenza A/H3N2 virus treated with baloxavir also had a shorter time to improve-

ment of symptoms (75.4 hours) versus those receiving placebo (100.4 hours, $P = 0.0141$). The median time to cessation of viral shedding in baloxavir-treated patients was 48 hours, versus less than 96 hours in both the placebo- and oseltamivir-treated patients. The incidence of serious adverse events did not significantly differ across groups.[13]

Adverse Effects

Adverse events were reported in 20.7% of baloxavir recipients, 24.6% of placebo recipients, and 24.8% of oseltamivir recipients in clinical trials. The most commonly reported adverse reactions from the two placebo-controlled trials included diarrhea (3%), bronchitis (2%), nasopharyngitis (1%), headache (1%), and nausea (1%).[11,12]

WARNINGS AND PRECAUTIONS

Baloxavir has no boxed warnings. Baloxavir only has efficacy against influenza viruses. Bacterial infections may present with influenza-like symptoms, or may coexist with or occur with influenza. Baloxavir cannot prevent these complications. Secondary bacterial infections should be managed and treated appropriately.[11]

SUPPLY/STORAGE/STABILITY/COST

Baloxavir is available as 20-mg and 40-mg tablets. The 20-mg tablets are white to light yellow, oblong-shaped, film-coated tablets debossed with an image and "772" on one side and "20" on the other side. The 40-mg tablets are white to light yellow, oblong-shaped, film-coated tablets debossed with "BXM40" on one side. Baloxavir should be stored in its blister package at 20°C to 25°C (68°F to 77°F) with temperature excursions permitted to 15°C to 30°C (59°F to 86°F). The price for a single dose is reported to be $150 but Genentech is currently offering a coupon for patients that reduces the price to $30.[11,14]

PATIENT COUNSELING

Patients should always read the FDA-approved patient information provided with their prescription. Advise patients to begin treatment with baloxavir as soon as possible within 48 hours of onset of influenza symptoms. The medication can be taken with or without food. Dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids, or oral supplements like calcium, iron, magnesium, selenium, or zinc, should not be taken with baloxavir. Patients should consult a health care provider before receiving a live, attenuated influenza vaccine after taking baloxavir because antivirals can decrease the efficacy of such vaccines. Common adverse effects may include diarrhea, bronchitis, nasopharyngitis, headache, and nausea.[11]

PLACE IN THERAPY

Baloxavir is a novel treatment for influenza that targets the polymerase complex of influenza A and B viruses. Its mechanism of action allows for use in patients who may have oseltamivir resistance. The efficacy and safety of combination therapy with baloxavir marboxil and a neuraminidase inhibitor in patients with severe influenza will be assessed in the NCT03684044 trial. Baloxavir is indicated for patients 12 years of age and older, which may limit its use in a younger population that is highly susceptible to influenza, as oseltamivir is approved for use in patients as young as 2 weeks old. Clinical benefits of baloxavir are similar to those of oseltamivir. Studies revealed that a single dose of baloxavir resulted in a shorter time to alleviation of symptoms and greater reductions in levels of influenza virus at one and two days after administration. However, it was also found that baloxavir induced viral escape mutants with reduced susceptibility. Infectious virus was detected five days after treatment in patients with mutations and those patients had a longer duration of influenza symptoms. Patients may be more adherent to baloxavir because only one dose is necessary for treatment as opposed to oseltamivir twice-daily dosing for five days. More information is needed regarding safety and efficacy in patients younger than 12 years old. The current two trials, NCT03653364 and NCT03629184, will assess the safety, pharmacokinetics, and efficacy in pediatric patients.[11,15]

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